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=> s receptor tyrosine kinase and bind
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L1        1462 RECEPTOR TYROSINE KINASE AND BIND

=> s receptor tyrosine kinase and bind?
L2        4509 RECEPTOR TYROSINE KINASE AND BIND?

=> s l2 and review/dt
L3         350 L2 AND REVIEW/DT

=> s l3 and py<1997
L4          95 L3 AND PY<1997

=> s l4 and receptor tyrosine kinase/ti
L5          16 L4 AND RECEPTOR TYROSINE KINASE/TI

=> d 1-16 bib ab

L5   ANSWER 1 OF 16     MEDLINE on STN
AN   97137748     MEDLINE
DN   PubMed ID: 8983085
TI   Non-receptor tyrosine kinases in mammalian
     neurogenesis.
AU   Aizawa S; Yagi T; Furuta Y; Ikawa Y; Nada S; Nakagawa H; Okada M
CS   Laboratory of Molecular Oncology Tsukuba Life Science Center, Ibaraki,
     Japan.
SO   Princess Takamatsu symposia, (1994) 24 323-37.  Ref: 67
     Journal code: 9301172.
CY   United States
DT   Journal; Article; (JOURNAL ARTICLE)
       General Review; (REVIEW)
     (REVIEW, TUTORIAL)
LA   English
FS   Priority Journals
EM   199705
ED   Entered STN: 19970609
     Last Updated on STN: 20000303
     Entered Medline: 19970529
AB   Several members of the Src family of non-receptor
     tyrosine kinases are expressed at high levels in
     embryonic neural tissues as well as in adult brain.  Relatively little has
     been known, however, about their roles in neural development.  Attempts to
     clarify this by production of mutant mice have been unsuccessful because
     of gene redundancy.  We earlier isolated a new cytoplasmic protein
     tyrosine kinase, Csk, and showed that it inactivates uniquely all members
     of non-receptor tyrosine kinases in vitro.
     Here, we have generated Csk-deficient mouse embryos and shown that Csk is
     indeed an indispensable negative regulator for all non-receptor
     tyrosine kinases in vivo, and that regulated activity of
     these kinases is essential for normal development of mice at the neural
     stage.  The signaling pathway through Src-family kinases during
     neurulation is also discussed.

L5   ANSWER 2 OF 16     MEDLINE on STN
AN   97012531     MEDLINE
DN   PubMed ID: 9156572
TI   Endosomes, receptor tyrosine kinase
     internalization and signal transduction.
AU   Bergeron J J; Di Guglielmo G M; Baass P C; Authier F; Posner B I
CS   Department of Anatomy and Cell Biology, McGill University, Montreal,
     Canada.
SO   Bioscience reports, (1995 Dec) 15 (6) 411-8.  Ref: 41
     Journal code: 8102797. ISSN: 0144-8463.
CY   United States
DT   Journal; Article; (JOURNAL ARTICLE)
       General Review; (REVIEW)
     (REVIEW, TUTORIAL)
LA   English
FS   Priority Journals
EM   199705
ED   Entered STN: 19970602
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Last Updated on STN: 20000303
Entered Medline: 19970522

AB Upon the **binding** of insulin or epidermal growth factor to their cognate receptors on the liver parenchymal plasmalemma, signal transduction and receptor internalization are near co-incident. Indeed, the rapidity and extent of ligand mediated receptor internalization into endosomes in liver as well as other organs predicts that signal transduction is regulated at this intracellular locus. Although internalization has been thought as a mechanism to attenuate ligand mediated signal transduction responses, detailed studies of internalized receptors in isolated liver endosomes suggest an alternative scenario whereby selective signal transduction pathways can be accessed at this locus.

L5 ANSWER 3 OF 16 MEDLINE on STN
AN 96422501 MEDLINE
DN PubMed ID: 8825118
TI Inhibition of signaling from Type 1 **receptor tyrosine kinases** via intracellular expression of single-chain antibodies.
AU Beerli R R; Wels W; Hynes N E
CS Friedrich Miescher Institute, Basel, Switzerland.
SO Breast cancer research and treatment, **(1996)** 38 (1) 11-7. Ref: 32
Journal code: 8111104. ISSN: 0167-6806.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 199611
ED Entered STN: 19961219
Last Updated on STN: 20000303
Entered Medline: 19961114

AB Members of the Type I/epidermal growth factor receptor (EGFR)-related family of **receptor tyrosine kinases** have been implicated in the development of human cancer. We have taken a novel approach using the intracellular expression of single chain antibodies (scFv) to specifically inhibit the in vivo action of these receptors. A scFv is a recombinant protein analogous to an Fv domain which is the smallest high affinity **binding** portion of an antibody. We report here on the expression in mammalian cells of cDNAs encoding scFv-225 and scFv-FRP5 directed against the extracellular domain of, respectively, human EGFR and human ErbB-2. The scFvs were provided with a signal peptide which directs them to the secretory pathway of the cell. scFv-225, which competes with EGF for **binding**, functions in an autocrine fashion to inhibit EGF-dependent cell growth. scFv-FRP5 was also provided with an endoplasmic reticulum (ER) retention signal and inactivates ErbB-2 in an intracrine fashion, by preventing its appearance on the cell surface.

L5 ANSWER 4 OF 16 MEDLINE on STN
AN 96421753 MEDLINE
DN PubMed ID: 8824370
TI Epidermal growth factor **receptor tyrosine kinase** inhibitors as potential cancer chemopreventives.
AU Kelloff G J; Fay J R; Steele V E; Lubet R A; Boone C W; Crowell J A; Sigman C C
CS Chemoprevention Branch, Division of Cancer Prevention and Control, National Cancer Institute, Bethesda, Maryland 20892, USA.
SO Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology, **(1996 Aug)** 5 (8) 657-66. Ref: 108
Journal code: 9200608. ISSN: 1055-9965.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)

LA English
FS Priority Journals
EM 199709
ED Entered STN: 19970922
Last Updated on STN: 20000303
Entered Medline: 19970909
AB Among the most important targets for chemopreventive intervention and drug development are deregulated signal transduction pathways, and protein tyrosine kinases are key components of these pathways. Loss of tyrosine kinase regulatory mechanisms has been implicated in neoplastic growth; indeed, many oncogenes code for either receptor or cellular tyrosine kinases. Because of its deregulation in many cancers (bladder, breast, cervix, colon, esophagus, head and neck, lung, and prostate), the epidermal growth factor receptor (EGFR) has been selected as a potential target for chemoprevention. Because growth factor networks are redundant, selective inhibition of signaling pathways activated in precancerous and cancerous cells should be possible. Requirements for specific EGFR inhibitors include specificity for EGFR, high potency, activity in intact cells, and activity in vivo. Inhibition of autophosphorylation is preferred, because it should result in total blockade of the signaling pathway. Inhibitors that compete with substrate rather than at the ATP-**binding** site are also preferable, because they are not as likely to inhibit other ATP-using cellular enzymes. Several classes of specific EGFR inhibitors have been synthesized recently, including structures such as benzylidene malononitriles, dianilinophthalimides, quinazolines, pyrimidines, [(alkylamino)methyl]-acrylophenones, enollactones, dihydroxybenzylaminosalicylates, 2-thioindoles, aminoflavones, and tyrosine analogue-containing peptides. A possible testing strategy for the development of these and other EGFR inhibitors as chemopreventive agents includes the following steps: (a) determine EGFR tyrosine kinase inhibitory activity in vitro; (b) evaluate EGFR specificity and selectivity (relative to other tyrosine kinases and other protein kinases); (c) determine inhibition of EGFR-mediated effects in intact cells; (d) determine inhibition of EGFR-mediated effects in vivo (e.g., in nude mouse tumor xenografts); and (e) determine chemopreventive efficacy in vivo (e.g., in the hamster buccal pouch or mouse or rat bladder).

L5 ANSWER 5 OF 16 MEDLINE on STN
AN 96074456 MEDLINE
DN PubMed ID: 7476307
TI Role of the time factor in signaling specificity: application to mitogenic and metabolic signaling by the insulin and insulin-like growth factor-I **receptor tyrosine kinases**.
AU De Meyts P; Christoffersen C T; Urso B; Wallach B; Gronskov K; Yakushiji F; Shymko R M
CS Department of Molecular Signaling, Hagedorn Research Institute, Gentofte, Denmark.
SO Metabolism: clinical and experimental, **(1995 Oct)** 44 (10 Suppl 4) 2-11. Ref: 88
Journal code: 0375267. ISSN: 0026-0495.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 199512
ED Entered STN: 19960124
Last Updated on STN: 20000303
Entered Medline: 19951220
AB The signal transduction pathways activated by hormones, growth factors, and cytokines show an extraordinary degree of cross-talk and redundancy. This review addresses the question of how the specificity conferred at the **binding** step is maintained through the signaling network despite the convergence of multiple signals on common efferent pathways such as mitogen-activated protein (MAP) kinase. The mechanism of receptor activation by ligand-induced dimerization provides a signaling device with both a switch and a timer. The role of the time factor, ie, of signaling kinetics, as a determinant of selectivity is discussed with emphasis on

the **receptor tyrosine kinases** and cytokine receptors, and especially mitogenic versus metabolic signaling by insulin and insulin-like growth factor-I (IGF-I).

L5 ANSWER 6 OF 16 MEDLINE on STN
AN 96063085 MEDLINE
DN PubMed ID: 7587067
TI Activation of Ras and other signaling pathways by **receptor tyrosine kinases.**
AU Schlessinger J; Bar-Sagi D
CS Department of Pharmacology, New York University Medical Center, New York 10016, USA.
SO Cold Spring Harbor symposia on quantitative biology, **(1994)** 59 173-9. Ref: 43
Journal code: 1256107. ISSN: 0091-7451.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 199511
ED Entered STN: 19960124
Last Updated on STN: 20000303
Entered Medline: 19951129

L5 ANSWER 7 OF 16 MEDLINE on STN
AN 95261697 MEDLINE
DN PubMed ID: 7743124
TI The first structure of a **receptor tyrosine kinase** domain: a further step in understanding the molecular basis of insulin action.
AU McDonald N Q; Murray-Rust J; Blundell T L
CS Department of Crystallography, Birkbeck College, London, UK.
SO Structure (London, England), **(1995 Jan 15)** 3 (1) 1-6. Ref: 39
Journal code: 9418985. ISSN: 0969-2126.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 199506
ED Entered STN: 19950621
Last Updated on STN: 20000303
Entered Medline: 19950612
AB Both the observed cis-inhibition and the proposed trans-activation of the insulin **receptor tyrosine kinase** help explain insulin signalling through its receptor.

L5 ANSWER 8 OF 16 MEDLINE on STN
AN 95201221 MEDLINE
DN PubMed ID: 7893993
TI Activation of Ras by **receptor tyrosine kinases**
.
AU Margolis B; Skolnik E Y
CS Department of Pharmacology, New York University Medical Center, NY 10016.
NC DK01927 (NIDDK)
SO Journal of the American Society of Nephrology : JASN, **(1994 Dec)** 5 (6) 1288-99. Ref: 125
Journal code: 9013836. ISSN: 1046-6673.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 199504
ED Entered STN: 19950504

Last Updated on STN: 20000303
Entered Medline: 19950427

AB Ras, a small GTP-**binding** protein, is an important component of the signal transduction pathway used by growth factors to initiate cell growth and differentiation. Cell activation with growth factors such as epidermal growth factor (EGF) induces Ras to move from an inactive GDP-bound state to an active GTP-bound state. Recently, a combination of genetic and biochemical studies has resulted in the elucidation of a signaling pathway that leads from growth factor receptors to Ras. After **binding** EGF, the EGF **receptor tyrosine kinase** is activated, leading to receptor autophosphorylation on multiple tyrosine residues. Signaling proteins with Src homology 2 (SH2) domains then **bind** to these tyrosine-phosphorylated residues, initiating multiple signaling cascades. One of these SH2 domain proteins, Grb2, exists in the cytoplasm in a preformed complex with a second protein, Son of Sevenless (Sos), which can catalyze Ras GTP/GDP exchange. After growth factor stimulation, the tyrosine phosphorylated EGF receptor **binds** the Grb2/Sos complex, translocating it to the plasma membrane. This translocation is thought to bring Sos into close proximity with Ras, leading to the activation of Ras. In contrast, the insulin receptor does not **bind** Grb2 directly but rather induces the tyrosine phosphorylation of two proteins, insulin receptor substrate-1 and Shc, that **bind** the Grb2/Sos complex. Once Ras is activated, it proceeds to stimulate a cascade of protein kinases that are important in a myriad of growth factor responses.

L5 ANSWER 9 OF 16 MEDLINE on STN
AN 95148687 MEDLINE
DN PubMed ID: 7846115
TI Inhibitors of the insulin **receptor tyrosine kinase**.
AU Srinivas P R; Grunberger G
CS Department of Internal Medicine, Wayne State University, Detroit, MI 48201.
NC DK 44382 (NIDDK)
SO Pharmacology & therapeutics, **(1994 Oct)** 64 (1) 23-35. Ref: 88
Journal code: 7905840. ISSN: 0163-7258.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 199503
ED Entered STN: 19950316
Last Updated on STN: 20000303
Entered Medline: 19950303

AB Insulin is a polypeptide hormone consisting of 51 amino acids. Insulin promotes a variety of anabolic enzymatic pathways and inhibits many catabolic enzymatic pathways involved in energy storage, as well as in synthesis of structural tissue proteins. In addition, insulin serves as a growth factor, modulating mitogenesis, growth and differentiation. Insulin mediates all of its effects by initially **binding** and activating its specific cell-surface receptor. Conformational changes induced by insulin **binding** lead to activation of intrinsic **receptor tyrosine kinase**. Thus, the study of tyrosine kinase inhibitors, whether synthetically produced or purified from microorganisms or humans, has led to elucidation of molecular details of physiological insulin signaling.

L5 ANSWER 10 OF 16 MEDLINE on STN
AN 94251115 MEDLINE
DN PubMed ID: 8193540
TI **Receptor tyrosine kinases** and their targets.
AU Kazlauskas A
CS Department of Pediatrics, National Jewish Center for Immunology and Respiratory Medicine, Denver, Colorado 80206.
NC CA55063 (NCI)
CA58187 (NCI)

GM48339 (NIGMS)
SO Current opinion in genetics & development, **(1994 Feb)** 4 (1) 5-14. Ref: 131
Journal code: 9111375. ISSN: 0959-437X.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LA English
FS Priority Journals
EM 199406
ED Entered STN: 19940707
Last Updated on STN: 20000303
Entered Medline: 19940630
AB One of the ways in which higher eukaryotes receive messages from the environment is via cell surface **receptor tyrosine kinases**. These are transmembrane proteins with an extracellular **binding** domain that specifies the growth factor with which it will interact, and an intracellular domain that encodes the tyrosine kinase. The mechanism by which **receptor tyrosine kinases** direct intracellular signal relay appears to involve receptor autophosphorylation that permits the stable **binding** of SH2 domain containing signal transduction enzymes. Some of the more recent advances are summarized in this review.

L5 ANSWER 11 OF 16 MEDLINE on STN
AN 94114591 MEDLINE
DN PubMed ID: 8286433
TI The role of p21ras in **receptor tyrosine kinase** signaling.
AU Medema R H; Bos J L
CS Laboratory for Physiological Chemistry, Utrecht University, The Netherlands.
SO Critical reviews in oncogenesis, **(1993)** 4 (6) 615-61. Ref: 470
Journal code: 8914610. ISSN: 0893-9675.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LA English
FS Priority Journals
EM 199402
ED Entered STN: 19940312
Last Updated on STN: 20000303
Entered Medline: 19940224
AB The notion that ras proteins are required for the stimulation of mitogenesis by different **receptor tyrosine kinases** (RTKs) has spurred researchers to investigate the precise role of p21ras in signal transduction. A large number of stimuli can drive p21ras in the active conformation, and several proteins that play an important role in regulating the GTP/GDP balance on p21ras have been identified. Indeed, activation of p21ras has been demonstrated to occur by stimulation of guanine nucleotide-releasing proteins (GNRPs) or inhibition of GTPase-activating proteins (GAPs). Moreover, a number of SH2-containing proteins have been implicated in this signaling pathway, such as shc and sem-5/grb2. On the other hand, downstream signaling from p21ras involves an important protein kinase cascade. This pathway seems to be conserved in evolution, and analogous routes have been described in organisms such as yeast, nematodes, and fruit flies. Nevertheless, the direct effector molecule of p21ras that could couple to this kinase cascade is still unknown. Some indications have been obtained that suggest that this function might be partially performed by p120GAP. This review gives an overview of the role of p21ras in signaling from diverse RTKs. Elucidation of this pathway will improve our understanding of mitogenic signaling pathways and the basis of cancer.

L5 ANSWER 12 OF 16 MEDLINE on STN
AN 93256917 MEDLINE
DN PubMed ID: 8387783

TI The assembly of signalling complexes by **receptor tyrosine kinases**.
AU Panayotou G; Waterfield M D
CS Ludwig Institute for Cancer Research, University College, Middlesex Hospital Branch, London, U.K.
SO BioEssays : news and reviews in molecular, cellular and developmental biology, **(1993 Mar)** 15 (3) 171-7. Ref: 78
Journal code: 8510851. ISSN: 0265-9247.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 199306
ED Entered STN: 19930618
Last Updated on STN: 19970203
Entered Medline: 19930607
AB Cell proliferation in response to growth factors is mediated by specific high affinity receptors. Ligand-**binding** by receptors of the protein tyrosine kinase family results in the stimulation of several intracellular signal transduction pathways. Key signalling enzymes are recruited to the plasma membrane through the formation of stable complexes with activated receptors. These interactions are mediated by the conserved, non-catalytic SH2 domains present in the signalling molecules, which **bind** with high affinity and specificity to tyrosine-phosphorylated sequences on the receptors. The assembly of enzyme complexes is emerging as a major mechanism of signal transduction and may regulate the pleiotropic effects of growth factors.

L5 ANSWER 13 OF 16 MEDLINE on STN
AN 93136666 MEDLINE
DN PubMed ID: 8380736
TI Isoforms of the met **receptor tyrosine kinase**.
AU Rodrigues G A; Park M
CS Department of Oncology and Medicine, McGill University, Montreal, Quebec, Canada.
SO EXS, **(1993)** 65 167-79. Ref: 50
Journal code: 9204529. ISSN: 1023-294X.
CY Switzerland
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 199302
ED Entered STN: 19930312
Last Updated on STN: 20000303
Entered Medline: 19930219
AB Hepatocyte growth factor/scatter factor (HGF-SF), a multifunctional cytokine, is the ligand for the met **receptor tyrosine kinase**. Multiple met mRNAs of 8, 7, 5, 3 and 1.6-kb in size have been identified in human cell lines and tissue. To investigate the biological function of these various isoforms we have isolated cDNA clones corresponding to some of the differentially spliced met mRNAs. Characterization of these cDNAs suggests that by alternative splicing and possibly by use of distinct transcription initiation sites the met HGF-SF receptor is expressed in various isoforms. We have demonstrated that there are two met 8-kb mRNAs that differ through alternative splicing of a 54-bp exon that maintains the open reading frame such that these proteins differ by only 18 aa in their extracellular domain. The -54-bp form corresponds to the most abundant 8-kb met RNA and encodes the p190 met alpha beta heterodimer. In contrast the +54-bp mRNA encodes a protein of 170 kd that is not cleaved yet is expressed at the cell surface and has in vitro kinase activity. The 7-kb mRNA differs by alternative splicing such that it encodes a protein with a distinct amino terminus. Unlike these met RNAs, the 1.6-kb mRNA has new 5' and 3' sequences and encodes a protein that shares homology with the extracellular domain of the met RTK

but has a unique carboxy terminus. Thus multiple met RNAs encode proteins that differ in both the extracellular ligand **binding** domain and within the cytoplasmic domain suggesting that these different met isoforms may have distinct biological activities.

L5 ANSWER 14 OF 16 MEDLINE on STN
AN 92184068 MEDLINE
DN PubMed ID: 1312047
TI **Receptor tyrosine kinases**.
AU Cadena D L; Gill G N
CS Department of Medicine, University of California, San Diego, La Jolla 92093-0650.
NC DK-07044-13 (NIDDK)
SO FASEB journal : official publication of the Federation of American Societies for Experimental Biology, **(1992 Mar)** 6 (6) 2332-7.
Ref: 47
Journal code: 8804484. ISSN: 0892-6638.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 199204
ED Entered STN: 19920424
Last Updated on STN: 19970203
Entered Medline: 19920416
AB A major process through which environmental information is transmitted into cells is via activation of protein tyrosine kinases. **Receptor tyrosine kinases** contain extracellular ligand recognition, single membrane spanning, and cytoplasmic protein tyrosine kinase domains. The cytoplasmic kinase core is flanked by regulatory segments, which in some family members are also inserted into the core kinase domain. Ligand **binding** initiates receptor signaling from the cell surface. Activated receptors autophosphorylate to remove alternate substrate/inhibitory constraints and to provide loci for assembly of proteins that contain SRC homology regions. Information is transmitted and diffused by tyrosine phosphorylation of the assembled proteins and of cellular substrates that include protein kinases with specificity for serine/threonine residues. Signaling, which is strictly ligand-dependent, is attenuated by down-regulation of receptors and by feed-back inhibitory loops that involve receptor phosphorylation by cellular kinases. The tyrosine kinase receptors are essential for normal growth, development, and reparative processes. Mutations that remove normal regulatory constraints on the approximately 290 amino acid kinase core of these large proteins result in constitutive function and cell transformation.

L5 ANSWER 15 OF 16 MEDLINE on STN
AN 90291867 MEDLINE
DN PubMed ID: 2162754
TI Insulin-**receptor tyrosine kinase** and glucose transport.
AU Lane M D; Flores-Riveros J R; Hresko R C; Kaestner K H; Liao K; Janicot M; Hoffman R D; McLenithan J C; Kastelic T; Christy R J
CS Department of Biological Chemistry, Johns Hopkins University School of Medicine, Baltimore, Maryland 21205.
NC NIDDK-14574 (NIDDK)
NIDDK-38418 (NIDDK)
SO Diabetes care, **(1990 Jun)** 13 (6) 565-75. Ref: 44
Journal code: 7805975. ISSN: 0149-5992.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 199007
ED Entered STN: 19900907

Last Updated on STN: 20000303
Entered Medline: 19900727

AB We identified the earliest events in autophosphorylation of the insulin receptor after insulin addition. Insulin-stimulated autophosphorylation at specific sites in the tyrosine kinase domain of the receptor's beta-subunit is correlated kinetically with activation of kinase-catalyzed phosphorylation of a model substrate (reduced and carboxyamidomethylated lysozyme; RCAM-lysozyme). To identify these sites, the deduced amino acid sequence of the 3T3-L1 adipocyte insulin receptor of the mouse was determined. Insulin-induced activation of substrate phosphorylation was shown to require autophosphorylation of three neighboring tyrosines (Tyr1148, Tyr1152, and Tyr1153) in the mouse receptor. A search for cellular substrates of the receptor kinase revealed that insulin causes accumulation of a 15,000-Mr phosphorylated (on tyrosine) cytosolic protein (pp15) in 3T3-L1 adipocytes treated with oxophenylarsine (PAO). PAO blocks turnover of the phosphoryl group of pp15, causing its accumulation, and thereby appears to interrupt signal transmission from the receptor to the glucose-transport system. Two membrane-bound protein phosphotyrosine phosphatases that are inhibited by PAO and are apparently responsible for the turnover of the pp15 phosphoryl group have been purified from 3T3-L1 adipocytes and characterized. These and other results support the hypothesis that turnover of the phosphoryl group of pp15, a product of insulin-**receptor tyrosine kinase** action, couples signal transmission to the glucose-transport system. [32P]pp15 was purified to homogeneity from 3T3-L1 adipocytes. Amino acid and radiochemical sequence analysis of the purified tryptic [32P]phosphopeptide revealed that pp15 is the phosphorylation product of 422(aP2) protein, a 15,000-Mr adipocyte protein whose cDNA we previously cloned and sequenced. 422(aP2) protein was found to **bind** fatty acids. When exposed to a free fatty acid, notably oleic acid, 422(aP2) protein becomes an excellent substrate of the isolated insulin-**receptor tyrosine kinase**. Compelling evidence indicates that on **binding** fatty acid, 422(aP2) protein undergoes a conformational change whereby Tyr19 becomes accessible to the **receptor tyrosine kinase** and undergoes O-phosphorylation. Adipose tissue and skeletal and heart muscle, which exhibit insulin-stimulated glucose uptake, express a specific insulin-responsive glucose transporter. A cDNA (GT2) that encodes this protein was isolated from a mouse 3T3-L1 adipocyte library and sequenced. We also isolated and characterized the corresponding mouse gene GLUT4. DNase I footprinting with nuclear extracts from 3T3-L1 cells revealed that a differentiation-specific nuclear factor **binds** to the GLUT4 promoter. The purified transcription factor C/EBP **binds** at the same position.(ABSTRACT TRUNCATED AT 400 WORDS)

L5 ANSWER 16 OF 16 MEDLINE on STN
AN 90197845 MEDLINE
DN PubMed ID: 2534271
TI Insulin **receptor**: **tyrosine kinase** activity and insulin action.
AU Ballotti R; Le Marchand-Brustel Y; Gammeltoft S; Van Obberghen E
CS INSERM U 145, Faculte de Medecine, Nice, France.
SO Reproduction, nutrition, development, **(1989)** 29 (6) 653-61.
Ref: 49
Journal code: 8913069. ISSN: 0926-5287.
CY France
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 199005
ED Entered STN: 19900601
Last Updated on STN: 20000303
Entered Medline: 19900510

AB The first step in insulin action consists in **binding** of the hormone to specific cell surface receptors. This receptor displays two functional domains: an extracellular alpha-subunit containing the majority or the totality of the hormone **binding** site and an intracellular

beta-subunit possessing insulin-stimulated tyrosine kinase activity. A general consensus has been reached in favour of the idea that this receptor enzymic function is essential for generation of the metabolic and growth-promoting effects of insulin. Concerning the mechanism of transmembrane signalling, we like to think that interaction of insulin with the receptor alpha-subunit triggers a conformational change, which is propagated to the beta-subunit and activates it. The active receptor kinase leads then to the phosphorylation of cellular protein substrates, which are likely to belong to two broad categories, those generating metabolic effects of insulin and those resulting in growth-promoting effects. The phosphorylated and active substrates then generate the final effects of insulin.